REMARKS

I. Overview

Applicants acknowledge the amendment and Information Disclosure Statement, filed May 15, 2008, have been entered and considered. Claims 5-23 and 26-29 stand withdrawn. Claims 1-4, 24, 25, 30 and 31 (as reading on Post-traumatic Stress Disorder) are pending and under examination. Applicants have amended Claims 1, 24, 25, 30 and 31 in scope with Applicants' species election. No new matter has been added to the claims. Support for the claim amendments can be found, for example, at least at page 16, starting at line 20, Figure 8 and of the originally filed specification, showing the relationship between treating anxiety conditions and demonstrated improvements in fear responses as tested by Applicants. Further, Applicants have further withdrawn Claim 4, placing all remaining pending claims in condition for allowance.

II. Withdrawn Claim Rejection - 35 U.S.C. § 112, Second Paragraph

Applicants acknowledge the Examiner's withdrawal of the rejection of Claim 30 under 35 U.S.C. §112, second paragraph, for being indefinite.

III. Claim Rejections - 35 U.S.C. § 112, first paragraph

A. Enablement

Claims 1-4, 24, 25, 30 and 31 stand rejected under 35 U.S.C. §112, first paragraph, as the Examiner states the specification does not enable a method of treatment for an anxiety disorder, such as Post-traumatic Stress Disorder (PTSD), by inhibiting an ASIC channel. The Examiner further states the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the

claims. The Examiner further explains that the claims recite a method of treatment for an anxiety disorder by administering an ASIC ion channel antagonist; however, no *in vivo* experiments were performed where ASIC receptors were inhibited or antagonized by adding a drug or antagonist.

Accordingly, the Examiner states the instant application does not reasonably provide enablement for a method of treating an anxiety disorder such as PTSD by administering an antagonist of the ASIC receptor. The Examiner emphasizes that no experiments were performed which measured changes in a disease such as PTSD, which is a uniquely human disease, and considered difficult to treat. The Examiner further stated that this is critically important since it is not known if all or many anxiety disorders are related to the ASIC receptor. Moreover, the Examiner states the specification is not enabling for a method of administering ASIC antagonists orally, topically, sublingually, buccally, intranasally, rectally or intravenously as there was no reduction to practice to support the claims.

Applicants respectfully traverse the Examiner's §112 rejections. As amended, Applicants' independent Claims 1, 24 and 30 are directed to methods of treating PTSD and disease states associated with pH changes and requiring improved fear responses. All claims have been amended commensurate in scope with Applicants' species election as well as the enabling written description.

Applicants' written description sets forth a variety of testing in mice with and without the ASIC receptors. Various testing was conducted related to the evaluation of fear conditioning. As defined in the originally filed specification, "fear conditioning" refers to the "process of acquiring, developing, educating, establishing, learning, or training responses in a patient having an identifiable stimulus including, but not limited to, apprehension, dread or alarm." (p. 7, lines 1-3). The results of fear conditioning with mice showed that ASIC -/- mice had decreased

reactions and responses to fear conditioning, such that decreases in behavior caused by fear were observed. *See for example,* FIGS. 8A-8D where the ASIC -/- mice had decreased freezing responses than ASIC +/+ mice. Further, the Examiner recognizes and appreciates the *in vitro* testing where ASIC channels were indeed antagonized by the manipulation of surrounding pH.

The testing for fear conditioning in mice obviates the Examiner's requirement for testing in humans. It is improper for the Examiner to require human testing for a "reduction to practice" of the present invention, merely because of the Examiner's opinion that PTSD is a "uniquely human disease, and considered difficult to treat." The treatment of PTSD inherently requires the study of one's response to fear, accordingly the studies conducted by Applicants in mice are relevant to and commensurate in scope with the amended claims.

The animal testing completed shows that the impact of fear conditioning is highly relevant to the modeling of treatment for PTSD in humans. Improvements in responses to fear are highly indicative of the similar measured changes in a disease such as PTSD. In fact, fear conditioning and fear-response studies are used in a wide variety of species, including both mice and humans. The differences between the testing of various species are namely the stimuli administered and the responses observed. In mice, freezing (period of immobility) or startled reactions (startle reflex due to a stimulus) are observed; whereas in humans, verbal responses are often measured. However, regardless of the species tested, fear conditioning is a method used to test the response of various treatments, including the use of ASIC antagonists as set forth in the present invention, which are not in fact unique to the single species tested. Accordingly, Applicants should not have a blanket rejection according to §112 enablement due to the lack of human testing. Rather, Applicants have satisfied the Examiner's requirement that either: (1) drugs be given *in vivo*; (2) humans be tested; and/or (3) adequate animal models of post-

traumatic stress disorder be tested. Here, Applicants have provided sufficient animal models for testing the anxiety condition commensurate in scope with the amended claims.

The Examiner also requires further explanation of a showing that ASIC receptor antagonists can be administered to treat anxiety disorders, namely PTSD to show there is a nexus between the ASIC receptor and PTSD. Applicants' originally filed specification sets forth the connection between anxiety disorders, as defined to include the fear-based disorders of PTSD, as well as the ASIC receptor and its underlying correlation. Based on this original support, and that known in the art by one having ordinary skill, Applicants have set forth for the Examiner the relationship between anxiety disorders and ASIC receptors. In addition, Applicants herein set forth support showing the correlation between ASIC and anxiety disorders known at the time of the invention. Namely, as set forth by Wemmie *et al.* (2004, as originally submitted in 2003), and included herein with the Information Disclosure Statement accompanying this Response, as well as related sources cited therein by Applicants, including for example, Wemmie *et al.* (2003) cited in the Information Disclosure Statement of May 15, 2008, and Olson *et al.* (1998) cited in the Information Disclosure Statement of September 10, 2003. These references confirm the presence of ASIC expression which is abundant in the various locations of the brain, including the amygdala complex, "which is required for fear conditioning and the expression of fear." (Wemmie *et al.* (2004) at page 3521). As previously set forth by Applicants, there is a clear relationship between fear conditioning and the expression of fear and post-traumatic stress disorder.

As a result of Applicants support the existing relationship between ASIC and anxiety conditions, such as the inherently fear-based condition of PTSD, as well as the sufficient use of experimentation in mice to determine fear-based responses, Applicants hereby respectfully

request the Examiner withdraw the §112 rejection and reconsider the claims to be placed in condition for allowance.

B. Written Description

Claims 1-4, 24, 25, 30 and 31 are also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner states that Claims 1-4, 24, 25, 30 and 31 are directed to methods of treating an anxiety disorder, such as PTSD, by inhibiting ASIC channels and that dependent claims recite pharmaceutical compositions comprising the ASIC receptor antagonist, as well as several routes of administration of the composition. The Examiner further states that the specification does not teach methods of treating an anxiety disorder in an animal, mammal or human. Still further, the Examiner states the description of methods of testing knockout mice behaviorally and of testing cells lacking the ASIC channel, is not adequate written description of a method of treating a uniquely human disease (PTSD), in human patients. Accordingly, the Examiner states that only methods of making and behaviorally testing ASIC knockout mice, and methods of antagonizing cultured neurons in vitro, but not the full breadth of the claims, meet the written description requirements of 35 U.S.C. §112.

Applicants respectfully traverse the Examiner's §112 rejections based on the written description requirement. First, Applicants direct the Examiner to the concomitantly filed Information Disclosure Statement providing the Coryell *et al.* reference discussed in and attached thereto Applicants' Office Action response of May 15, 2008. The Coryell *et al.* reference is titled *Targeting ASIC1a Reduces Innate Fear and Alters Neuronal Activity in the Fear Circuit*, and

was published in Biol. Psychiatry. 62(10):1140-8 (2007) and is included for the Examiner's review, showing ASIC antagonists.

The Examiner acknowledges that the specification discloses experiments confirming the role of ASIC1 receptors in fear conditioning and short-term memory. Accordingly, in order to expedite prosecution, Applicants have amended the pending independent claims so that the full breadth of the claims meet the written description requirements of §112 as set forth by the Examiner. Claim 1 is amended so that it now recites "A method of treatment for post-traumatic stress disorder comprising: administering to a patient in need thereof a therapeutically effective amount of an acid sensing ion channel (ASIC) antagonist and a pharmaceutically acceptable carrier, wherein said antagonist causes improved fear responses."

Claim 24 is amended to now recite "A method of treating a disease state associated with increased pH which comprises: administering to a patient a therapeutically effective amount of an acid sensing ion channel (ASIC) antagonist capable of improving fear responses and a pharmaceutically acceptable carrier." Further, Claim 30 is amended so that it now recites "A method of treating a CNS disorder characterized by a change in extracellular pH in the amygdala comprising: inhibiting the acid-sensing ion channel 1 (ASIC1) in order to improve fear responses in a patient in need of such treatment."

Applicants respectfully submit that amended claims 1, 24 and 30 overcome the Examiner's rejection as the causation of improved fear responses is a necessary element of treating PTSD and is clearly supported in the Applicant's originally filed specification, as addressed above under Section III-A "Enablement." The effect of ASIC receptors on fear responses, as set forth in the above-described fear conditioning examples has been acknowledged by the Examiner as being a condition involving the ASIC receptor.

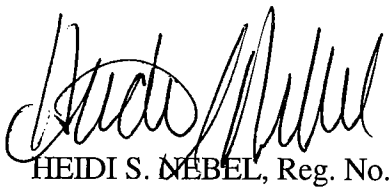
Additionally, Applicants' claim amendments highlighting the necessity for improved fear responses in order to treat PTSD obviates the Examiner's statement that a skilled artisan could not "envision the detailed methods needed to treat an anxiety disorder by administering an ASIC antagonist." To the contrary, Applicants have shown positive improvements through the use of animal models sufficient for predicting success in humans, according to approaches set forth by Price *et al.*, Nature 407:1007-1011 (2000) as incorporated by reference into the originally filed specification. (p. 26, Examples "Materials and Methods").

As a result, Applicants hereby respectfully request the Examiner withdraw the §112 rejection and reconsider the claims to be placed in condition for allowance.

IV. Conclusion

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Respectfully submitted,



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